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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,226	01/11/2002	Bernd Riedl	BAYER 25A	5076

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EXAMINER	
JONES, DWAYNE C	

ART UNIT	PAPER NUMBER
1614	

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16

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/042,226	RIEDL ET AL.	
	Examiner	Art Unit	
	Dwayne C Jones	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-13,15,17-19,21,27,28,32,33,37-39,43-50,52-54 and 66-121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *14*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-3, 6-13, 15, 17-19, 21, 27, 28, 32, 33, 37-39, 43-50, 52-54, and 66-121.

DETAILED ACTION

Status of Claims

1. Claims 1-3, 6-13, 15, 17-19, 21, 27, 28, 32, 33, 37-39, 43-50, 52-54, and 66-121 are pending.

2. Claims 1-3, 6-13, 15, 17-19, 21, 27, 28, 32, 33, 37-39, 43-50, 52-54, and 66-121 are rejected.

Information Disclosure Statement

3. The information disclosure statement filed on September 22, 2003 has been reviewed and considered, see enclosed copy of PTO FORM 1449.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3, 6-13, 15, 17-19, 21, 27, 28, 32, 33, 37-39, 43-50, 52-54, and 68-87, and 91-120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. There is a lack of written description in the specification, as well as the instant claims for the various types of variables that are embraced by the compound of Formula

(I). The claimed methods of treatment fail meet the requirement for an adequate written description of the claimed invention as required by 35 U.S.C. 112, first paragraph. In addition, the instant specification does not describe what is meant by the phrase the various definitions for the variables of A, B, R_y, R_z, R_x. For example, the variable of A, for instance with the phrase "substituted moiety of up to 40 carbon atoms. . . "

7. Claims 1-3, 6, 8, 10-13, 15, 17-19, 21, 27, 28, 32, 33, 37-39, 43-50, 52-54, and 66-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

8. There is insufficient descriptive support for the phrase treatment of cancerous cell growth mediated by RAF kinase as well as the treatment of solid cancers and the treatment of carcinomas, myeloid disorders or adenomas. The claimed methods of treatment fail meet the requirement for an adequate written description of the claimed invention as required by 35 U.S.C. 112, first paragraph. In addition, the instant specification does not describe what is meant by the phrase treatment of cancerous cell growth mediated by RAF kinase as well as the treatment of solid cancers and the treatment of carcinomas, myeloid disorders or adenomas. Structural identifying characteristics of the phrase treatment of cancerous cell growth mediated by RAF kinase as well as the treatment of solid cancers and the treatment of carcinomas, myeloid disorders or adenomas. There is no evidence that there is any per se

structure/function relationship between the phrase treatment of cancerous cell growth mediated by RAF kinase as well as the treatment of solid cancers and the treatment of carcinomas, myeloid disorders or adenomas The instant specification does provide an adequate written description for the phrase treatment of cancerous cell growth mediated by RAF kinase as well as the treatment of solid cancers and the treatment of carcinomas, myeloid disorders or adenomas. In the absence of some understanding of the conditions to be treated one of ordinary skill in the art would not have concluded that Applicant was in possession of the claimed methods. Accordingly, these claims fail to comply with the written description requirement.

9. Claims 7, 9 and 90-121 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. There is insufficient descriptive support for the phrase the treatment of a raf mediated disorder. The claimed methods of treatment fail meet the requirement for an adequate written description of the claimed invention as required by 35 U.S.C. 112, first paragraph. The claimed methods require treatment of an unspecified disease or disorder and no evidence indicates that a treatable disease was known to Applicants. In addition, the instant specification does not describe what is meant by the phrase the treatment of a raf mediated disorder. Structural identifying characteristics of the phrase the treatment of a raf mediated disorder There is no evidence that there is any per se

structure/function relationship between the phrase the treatment of a raf mediated disorder The instant specification does provide an adequate written description for the phrase the treatment of a raf mediated disorder. In the absence of some understanding of the conditions to be treated one of ordinary skill in the art would not have concluded that Applicant was in possession of the claimed methods. Accordingly, these claims fail to comply with the written description requirement.

11. *Regents of the University of California v. Eli Lilly & Co.., 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S.Ct. 1548 (1980),* holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly, 119 F.3d at 1566.* The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for *Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001)*, which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, "including, inter alia, "functional characteristics when coupled with a known or disclosed correlation between function and structure...." *Enzo Biochem, Inc. v. Gen-Probe., 296 F.3d, 316, 1324-25 (Fed. Cir. 2002)* (quoting Guidelines, 66 Fed. Reg. At 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical

structures in general. *Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp.2d 216, 225 (W.D.N.Y 2003).*

12. Claims 1-3, 6-13, 15, 17-19, 21, 27, 28, 32, 33, 37-39, 43-50, 52-54, and 66-121 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *in vitro* treatment of the tumor cell lines of HCT116 and DLD-1, does not reasonably provide enablement for the treating of all types of cancers, solid cancers, carcinomas, myeloid disorders, adenoma, and cancerous cells, and disorders mediated by raf. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to the treating of all types of cancers, solid cancers, carcinomas, myeloid disorders, adenoma, and cancerous cells, and disorders mediated by raf. The method comprises administering the compounds of Formula (I).

(2) The state of the prior art

The compounds of the inventions are compounds of Formula (I). However, the prior art teaches that there are many types of cancers and various causative agents that involve different cellular mechanisms, and, for thus, differ in treatment protocol, see Stein, J. H.

(3) The relative skill of those in the art

The relative skill of those in the art of cancer pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24 (CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court

held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art0; In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of the urea-containing compounds prior to filing of the instant invention was an unpredictable art.

(5) The breadth of the claims

The instant claims are very broad. For instance, claim 1 is directed to the plethora of compounds of Formula (I) and for treating of all types of cancers, solid cancers, carcinomas, myeloid disorders, adenoma, and cancerous cells, and disorders mediated by raf. The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.),cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein

structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of the physiological or pharmaceutical activity of a Formula (I) to be effective in treating of all types of cancers, solid cancers, carcinomas, myeloid disorders, adenoma, and cancerous cells, and disorders mediated by raf is insufficient for enablement. The specification provides no guidance, in the way of enablement for treating of all types of cancers, solid cancers, carcinomas, myeloid disorders, adenoma, and cancerous cells other than the *in vitro* treatment of the tumor cell lines of HCT116 and DLD-1. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and

electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses the compounds of Formula (I) that have the ability of treating of all types of cancers, solid cancers, carcinomas, myeloid disorders, adenoma, and cancerous cells, and disorders mediated by raf. However, the instant specification only has enablement for the *in vitro* treatment of the tumor cell lines of HCT116 and DLD-1.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the generic group of compounds of Formula I that are used in that would be enabled in this specification.

Obviousness-type Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1-3, 6-13, 15, 17-19, 21, 27, 28, 32, 33, 37-39, 43-50, 52-54, and 66-121 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 62-67 are of copending Application No. 09/948,915. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are directed to the treatment of cancerous cell growth with urea containing compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 1-3, 6-13, 15, 17-19, 21, 27, 28, 32, 33, 37-39, 43-50, 52-54, and 66-121 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29, 30, 32, and 33 of copending Application No. 09/777,920. Although the conflicting claims are not identical, they are not patentably distinct from each other because to the treatment of cancerous cell growth with urea containing compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Thursday, and Fridays from 8:30 am to 6:00 pm. The official fax No. for correspondence is (703) 872-9306.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, may be reached at (571) 272-0584.

DWAYNE JONES
PRIMARY EXAMINER

Tech. Ctr. 1614
March 20, 2004